Elucidating 1st & 2nd-Order Parametric Effects in PBPK Models for Special Scenarios Using a GSA-based Approach

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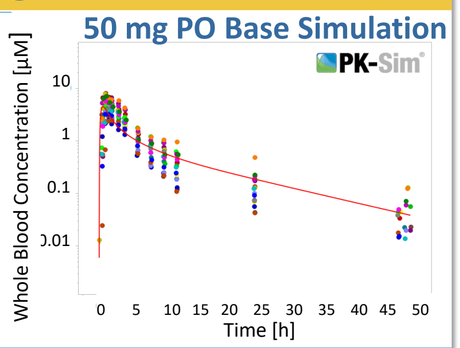
BACKGROUND

- The ≥**65-year-old population** is subject to a host of physiological and lifestyle changes that can affect drug absorption.
- The BCS II/IV drug **Danirixin** (DNX) shows differences in pharmacokinetics (PK) due to factors including age, food and PPI usage.
- **PBPK models** can be used to investigate such scenarios, but alone may be limited in identifying which factors are important or negligible to drug absorption.
- A joint **PBPK-GSA (Global Sensitivity Analysis)** approach can resolve such needs, as they quantify each factor's contribution to output variation, account for higher-order effects, but often cannot identify important inter-parametric relationships.
- The **Cycle Equitable-based (CEQ) sampling scheme**[1] for the **Morris Method** estimates higher-order effects and the nature of the interaction with computational effiency.

AIM: Build a Full-PBPK Danirixin Model and Estimate the Risk of PK Deviations by Analyzing Inter-Parametric Relationships

METHODS

1 Developed full-PBPK model for Danirixin HBr (DNX HBr) salt in older people



2 Custom integration of CEQ-based design in R for analysis of higher order effects on PK[2]

3 Model scenarios were tested :

4 Key Absorption Factors from Legacy Study[3]
Solubility: ±50%
Int. Perm: 50-100%
Gastric pH: 0.5-6.5
Gastric emptying time: 40-400%

Healthy Variation in Upper Intestinal Physiology
pH: ±0.5
other: ±15%

PPI Influence on Upper Intestinal Physiology
From previous setup,
Gastric pH: 4-6.5
Duodenal pH: 6-7
Gastric emptying time: 100-150%

Generate sampling matrix
For simultaneous assessment of 1st and 2nd order effects using a recursive cyclic design[1]
(# trajectories= 30, Δ = 0.3)

Inverse Transform Sampling
Uniform probability distributions ↔ [0,1]

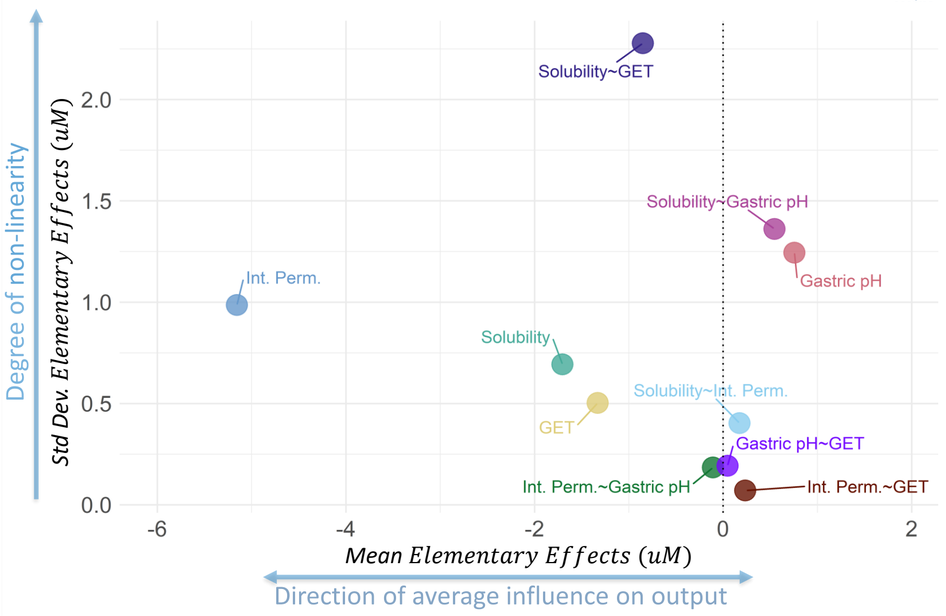
Batch Simulations
330-4110 simulations, 5 per batch using *for* loop
Dell Latitude 5320, Intel Core I5

Calculation of Elementary Effects
and graphical analysis

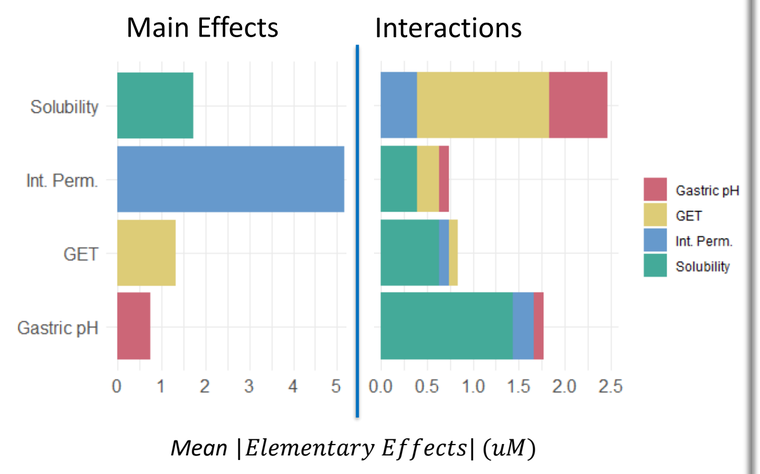
RESULTS

Analysis of Key Parameters

1st & 2nd Order Effects of Gastric pH, Solubility, Intestinal Permeability (Int. Perm.) and Gastric Emptying Time (GET) on C_{max}



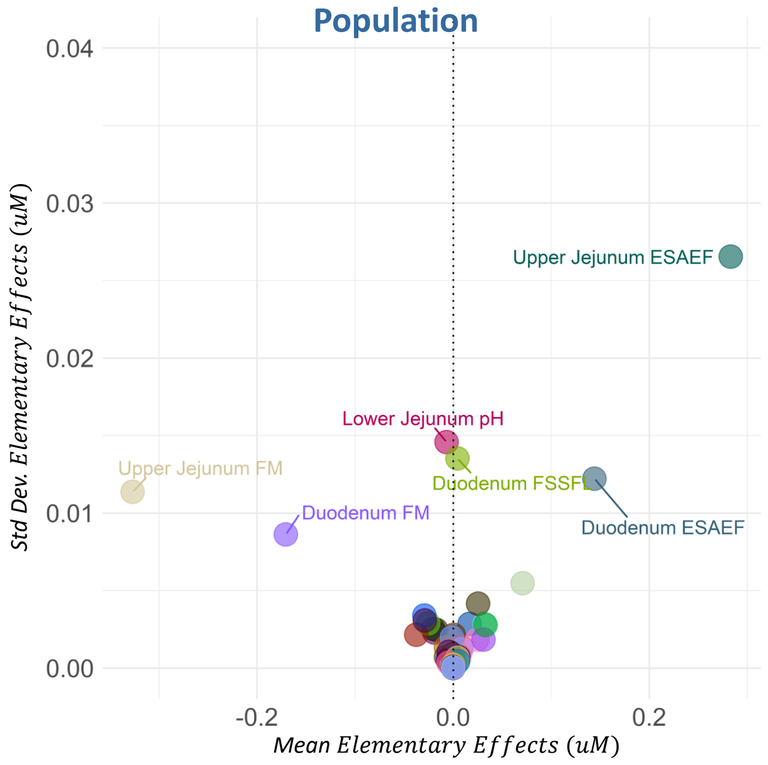
Magnitude of Parametric Influences on C_{max}



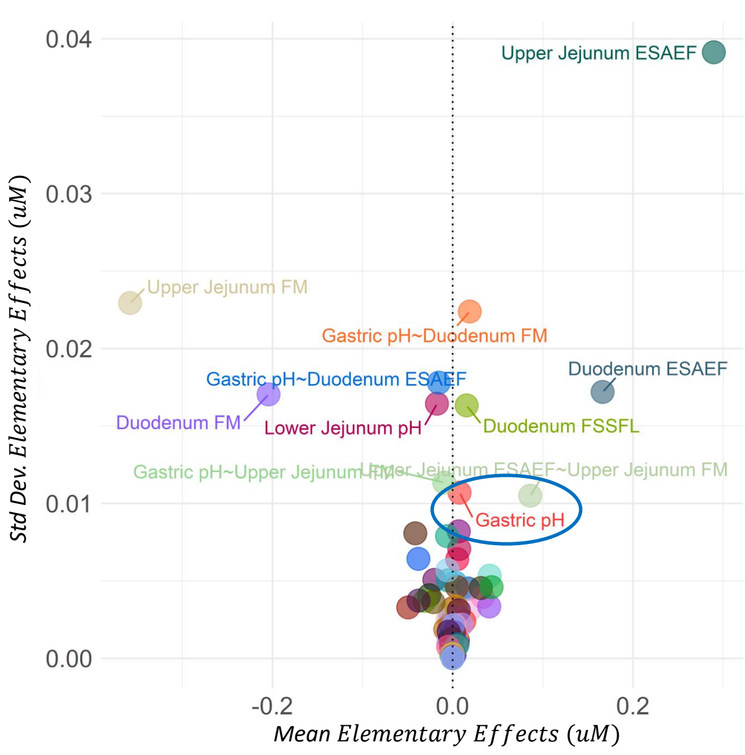
Uncertainty in physicochemical parameters largely influences C_{max}. Despite Intestinal Permeability having the largest direct effect, Solubility is the major interacting parameter and should also be prioritized.

Analysis of Upper Intestinal Physiology

Major Influences Driving Variation in a Healthy Population

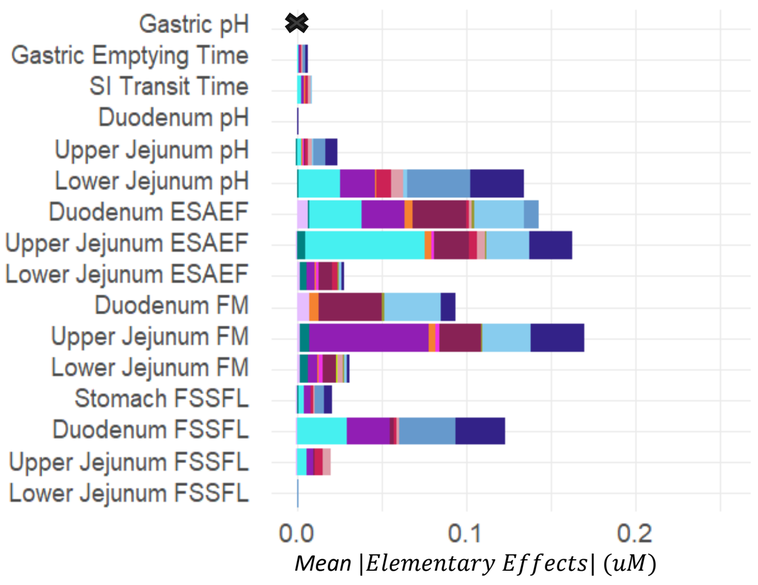


Major Influences Driving Variation in a PPI Population

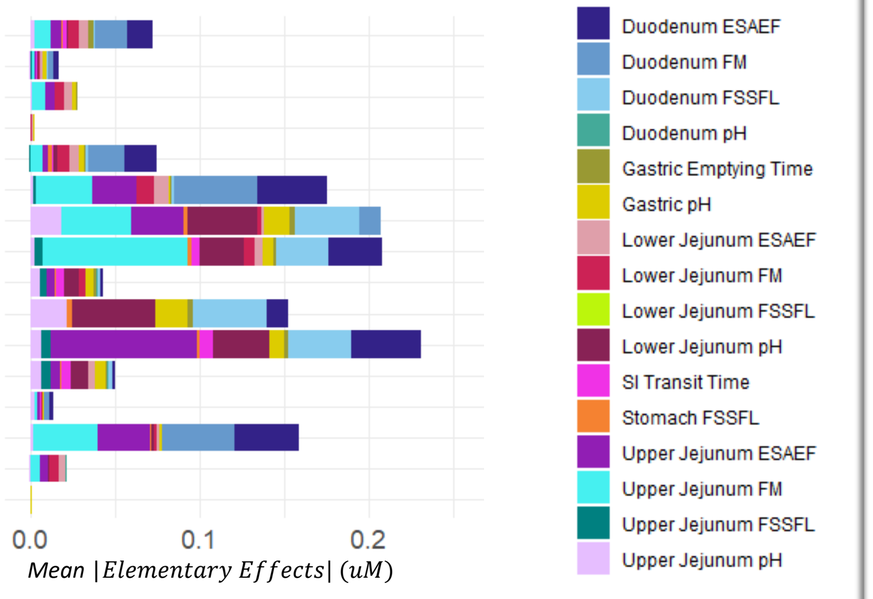


Effective Surface Area Enhancement Factors (ESAEFs) and Fraction Mucosa (FM) are the most influential on C_{max} for both the healthy and PPI variations. The increase in standard deviation for Gastric pH in the PPI configuration indicates increased importance via higher-order effects, which is confirmed in the bar plots below. (FSSFL: Fractional Steady-State Fill Levels)

Pairwise Interactions in a Healthy Population



Pairwise Interactions in a PPI Population



Gastric pH shows the greatest difference of the 3 parameters changed between healthy and PPI configurations. According to both the scatter and bar plots, the duodenal surface area and mucosal volume modulate the variation in C_{max} due to Gastric pH. Nevertheless, the top parameters remain the same and their distributed elementary effects reflect minimal overall changes in C_{max} for DNX HBr (*ie.* robustness of the formulation to elevated gastric pH).

CONCLUSION

- Results for this case study are consistent with other SA techniques but provided more in-depth information into the model's contextual parametric relationships.
- The CEQ-Morris design successfully estimated parametric 1st and 2nd-order effects and provided deeper insight into the relative importance of each interaction.
- The method can be used to evaluate mechanisms behind changes in model behavior for special scenarios, verify assumptions and identify key parameters for risk mitigation.

REFERENCES

1. Fédou & Rendas 2015. Jour of Stat Comp and Sim, 85:7, 1398-141
2. Robins et al. 2023. ACOP, *Poster*
3. Lloyd et al. 2020. In Pharm research 37 (12), p. 233

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